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=> s monomeric protein
L1         5449 MONOMERIC PROTEIN

=> s l1 and TGF beta superfamily
L2            1 L1 AND TGF BETA SUPERFAMILY

=> d l2 cbib abs

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
2001:98512   Document No. 134:142803  Method for producing human
     monomeric proteins of the TGF-beta family. (Mader &
     Baumgartner Treuhand A.-G., Switz.).  Eur. Pat. Appl. EP 1074620 A1
     20010207, 31 pp.  DESIGNATED STATES: R:  AT, BE, CH, DE, DK, ES, FR, GB,
     GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO.  (English).
     CODEN: EPXXDW.  APPLICATION: EP 1999-115613 19990806.
AB   The present invention is concerned with a method for producing human
     proteins selected from the members of the TGF-β
     superfamily, which are monomeric due to substitution or deletion
     of a cysteine which is responsible for dimer formation.  The invention is
     also concerned with nucleic acids, encoding such monomeric
     proteins, vectors or host cells containing the nucleic acids as well
     as with pharmaceutical compns. comprising the proteins or nucleic acids
     encoding the proteins.  The pharmaceutical compns. can be applied
     advantageously for all indications for which the resp. dimeric proteins
     are useful.


=> s TGF beta superfamily
L3         5269 TGF BETA SUPERFAMILY

=> s l3 and monomeric
L4           12 L3 AND MONOMERIC

=> dup remove l4
PROCESSING COMPLETED FOR L4
L5             4 DUP REMOVE L4 (8 DUPLICATES REMOVED)

=> d l5 1-4 cbib abs

L5   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
2002:428931   Document No. 137:10949  Production of recombinant bone
     morphogenetic protein BMP-2.  Rudolph, Rainer; Schwarz, Elisabeth; Herr,
     Gerhard; Hillger, Frank (Scil Proteins Gmbh, Germany).  PCT Int. Appl. WO
     2002044203 A2 20020606, 49 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT,
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AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2001-EP13840 20011127. PRIORITY: DE 2000-10059336 20001129.

AB In order to recombinantly produce a biol. active protein of the **TGF** β **superfamily**, a protein is expressed in prokaryotes. The amino terminus of this expressed protein consists of the prosequence of a protein of the **TGF** β **superfamily** or portions thereof, to which the mature domain of this protein or of another protein of the **TGF** β **superfamily** is joined, said protein having at least 35 % homol. to mature BMP-2. The expression of the protein is carried out under conditions in which at least one portion of the protein is obtained in the form of inclusion bodies. The inclusion bodies are isolated and are solubilized under denaturing conditions. The denatured, **monomeric** and biol. inactive protein, which is solubilized from the inclusion bodies, is natured while folding and dimerizing to the soluble, biol. active conformation and, optionally, the mature protein is proteolytically released from its proform after naturation.

L5 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

2001:98512 Document No. 134:142803 Method for producing human **monomeric** proteins of the TGF-beta family. (Mader & Baumgartner Treuhand A.-G., Switz.). Eur. Pat. Appl. EP 1074620 A1 20010207, 31 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-115613 19990806.

AB The present invention is concerned with a method for producing human proteins selected from the members of the **TGF**-β **superfamily**, which are **monomeric** due to substitution or deletion of a cysteine which is responsible for dimer formation. The invention is also concerned with nucleic acids, encoding such **monomeric** proteins, vectors or host cells containing the nucleic acids as well as with pharmaceutical compns. comprising the proteins or nucleic acids encoding the proteins. The pharmaceutical compns. can be applied advantageously for all indications for which the resp. dimeric proteins are useful.

L5 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 1

2001274360. PubMed ID: 11278594. The propeptide of the transforming growth factor-beta superfamily member, macrophage inhibitory cytokine-1 (MIC-1), is a multifunctional domain that can facilitate protein folding and secretion. Fairlie W D; Zhang H P; Wu W M; Pankhurst S L; Bauskin A R; Russell P K; Brown P K; Breit S N. (Centre for Immunology, Saint Vincent's Hospital and University of New South Wales, Victoria Street, Sydney, New South Wales 2010, Australia.) Journal of biological chemistry, (2001 May 18) 276 (20) 16911-8. Electronic Publication: 2001-02-26. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Macrophage inhibitory cytokine-1 (MIC-1) is a divergent member of the transforming growth factor-beta (**TGF-beta**) **superfamily.** While it is synthesized in a pre-pro form, it is unique among superfamily members because it does not require its propeptide for correct folding or secretion of the mature peptide. To investigate factors that enable these propeptide independent events to occur, we constructed MIC-1/TGF-beta1 chimeras, both with and without a propeptide. All chimeras without a propeptide secreted less efficiently compared with the corresponding constructs with propeptide. Folding and secretion were most affected after replacement of the predicted major alpha-helix in the mature protein, residues 56-68. Exchanging the human propeptide in this chimera with either the murine MIC-1 or TGF-beta1 propeptide resulted in secretion of the unprocessed, **monomeric**

chimera, suggesting a specific interaction between the human MIC-1 propeptide and mature peptide. Propeptide deletion mutants enabled identification of a region between residues 56 and 78, which is important for the interaction between the propeptide and the mature peptide. Cotransfection experiments demonstrated that the propeptide must be in cis with the mature peptide for this phenomenon to occur. These results suggest a model for **TGF-beta superfamily** protein folding.

L5 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 2
94308219. PubMed ID: 8034704. **Monomeric** activin A retains high receptor binding affinity but exhibits low biological activity. Husken-Hindi P; Tsuchida K; Park M; Corrigan A Z; Vaughan J M; Vale W W; Fischer W H. (Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, California 92037.) Journal of biological chemistry, (1994 Jul 29) 269 (30) 19380-4. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Activins are multipotent hormones/growth factors that belong to the transforming growth factor-beta (**TGF-beta**) **superfamily.** Like TGF-beta s, activins have 9 conserved cysteine residues and are disulfide-bonded dimers. Based on the three-dimensional structure of TGF-beta 2, we deduced Cys80 in activin A to form the intermolecular disulfide bond. To obtain a **monomeric** form of activin, Cys80 was exchanged for a serine residue by polymerase chain reaction mutagenesis. The mutant protein was expressed in a baculovirus/insect cell expression system. The molecular mass of this mutant activin was determined to be 13 kDa (consistent with a single chain form of the protein) by SDS-polyacrylamide gel electrophoresis and by laser desorption mass spectroscopy. When this mutant **monomeric** activin was incubated with cells that expressed either the activin type IIB receptor or both the type I and type IIB receptors, its affinity was found to be 20% of that of native activin on a mass basis. Binding affinity determined using the mouse pituitary cell line AtT 20 was 10% of that of native activin A. Biological potency, however, as determined by the mutant protein's ability to release FSH from anterior pituitary cells in primary culture and by its ability to suppress basal ACTH secretion form AtT 20 cells, was only 1% of that of the native protein. This discrepancy of an order of magnitude between binding and biological activity is consistent with a model in which dimerization of the hormone is not necessary for high affinity binding to its receptor(s) while being essential for efficient signal transduction.

=> s human MP52
L6 13 HUMAN MP52

=> s l6 and substitution
L7 0 L6 AND SUBSTITUTION

=> dup remove l6
PROCESSING COMPLETED FOR L6
L8 12 DUP REMOVE L6 (1 DUPLICATE REMOVED)

=> d l8 1-12 cbib abs

L8 ANSWER 1 OF 12 MEDLINE on STN DUPLICATE 1
2005217929. PubMed ID: 15850370. Use of osteopromotive growth factors, demineralized bone matrix, and ceramics to enhance spinal fusion. Khan Safdar N; Fraser Justin F; Sandhu Harvinder S; Cammisa Frank P Jr; Girardi Federico P; Lane Joseph M. (Department of Orthopaedic Surgery, University of California at Davis, Sacramento, CA, USA.) Journal of the American Academy of Orthopaedic Surgeons, (2005 Mar-Apr) 13 (2) 129-37. Ref: 33. Journal code: 9417468. ISSN: 1067-151X. Pub. country: United States. Language: English.
AB Recently developed materials that can enhance fusion rates for

posterolateral lumbar arthrodesis may be used alone or in combination with autogenous bone grafts. Novel osteopromotive growth factor preparations are currently under scrutiny; these include autogenous growth factor concentrate, bovine bone-derived osteoinductive protein, and recombinant **human MP52.** Demineralized bone matrix products may enhance or extend grafts. However, few studies, especially prospective randomized clinical trials, have assessed their efficacy, so it is difficult to compare formulations. Ceramics have been evaluated in animal studies and human clinical trials for a variety of applications in spinal surgery. These materials function best as bone graft extenders or as bioactive osteoinductive material carriers in posterolateral lumbar fusions. They have the advantage of variable porosity, low cost, and ease of manufacture. Hydroxyapatite/tricalcium phosphate ceramics have been shown to perform as well as autogenous bone grafts but with fewer complications.

L8 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2004:550724 Document No. 141:76794 Lyophilized composition of bone morphogenetic factor **human MP52.** Ichikawa, Hideki; Inagaki, Mitsuko (Biopharm G.m.b.H., Germany). U.S. Pat. Appl. Publ. US 2004132653 A1 20040708, 4 pp., Cont.-in-part of U.S. Ser. No. 355,551, abandoned. (English). CODEN: USXXCO. APPLICATION: US 2003-666535 20030922. PRIORITY: JP 1997-16349 19970130; WO 1998-JP371 19980129; US 1999-355551 19990921.

AB By mixing bone morphogenetic factor **human MP52** with mannitol at a weight ratio of 1:5-50, followed by lyophilization, a stable lyophilized composition of bone morphogenetic factor **human MP52** is obtained which prevents coloring and atrophy of the lyophilized product of bone morphogenetic factor **human MP52** during storage and also prevents cohesion at the time of reconstitution. To 1 mg/mL of an aqueous solution of purified rhMP52, 10, 25, and 50 mg, D-mannitol was added. After the resulting mixture was filtered through a 0.22-μm membrane filter, 1 mL portions of the filtrate so obtained were filled in vials in a sterile fashion. They were lyophilized, whereby a composition of the present invention was prepared in the form of pharmaceutical product.

L8 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2002:113762 Document No.: PREV200200113762. Anti-**human MP52** monoclonal antibody. Kitagawa, Hiroshi [Inventor, Reprint author]; Jitsukawa, Tomofumi [Inventor]; Nakagawa, Hiraku [Inventor]; Yanagisawa, Sachiko [Inventor]. Saitama, Japan. ASSIGNEE: Hoechst Marion Roussel, France. Patent Info.: US 6328963 20011211. Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 11, 2001) Vol. 1253, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB A mouse anti-**human MP52** monoclonal antibody which binds to dimeric **human MP52** but not to monomeric **human MP52.** This mouse monoclonal antibody comprising IgG and having a high specificity can be obtained by sensitizing mice with **human MP52** (CHO-MP52) produced in CHO cells and **human MP52** (rhMP52) produced in escherichia coli. This antibody is useful in, for example, purifying or assaying **human MP52** produced b genetic engineering techniques.

L8 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2000:260344 Document No. 132:289232 Bone morphogenetic protein antagonist based on the mature protein. Katsuura, Mieko; Kimura, Michio (Hoechst Marion Roussel, Fr.). PCT Int. Appl. WO 2000021998 A1 20000420, 40 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO

1999-IB1621 19991004. PRIORITY: JP 1998-288103 19981009.

AB The purpose is to provide a mature protein having an antagonistic activity against bone morphogenetic proteins. The mature protein having an antagonistic activity against bone morphogenetic proteins is obtained by converting at least one residue among methionine residues or tryptophane residues existing in the amino acid sequence of mature **human MP52** to a hydrophilic residue by chemical modification, or replacing said residues with a hydrophilic amino acid residue or a polar amino acid residue. The chemical modification for said methionine residue is performed by an oxidization reaction or an alkylation reaction. The chemical modification for said tryptophane residue is performed by an allylsulfenylation reaction. Or a mature protein having an antagonistic activity against bone morphogenetic proteins is obtained by converting at least one residue of tryptophane residues existing in the amino acid sequences of mature human BMP-2 , mature human BMP-4 , and mature human BMP-7 to a hydrophilic residue by chemical modification, or replacing said residues with a hydrophilic amino acid residue or a polar amino acid residue. The BMP antagonists are used for therapy or prevention of ectopic ossification or metabolic diseases with calcification.

L8 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2000:80055 Document No. 132:119568 An efficient method for purifying bone morphogenetic protein. Kimura, Michio; Ohsawa, Kayoko; Fujino, Yukio (Hoechst Marion Roussel K. K., Japan). Jpn. Kokai Tokkyo Koho JP 2000034298 A2 20000202, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1998-203092 19980717.

AB A convenient and efficient method is provided for purifying and recovering a large amount of bone morphogenetic protein from the animal cell culture medium supernatant containing bone morphogenetic protein expressed by a genetic engineering technique. The purification method comprises a process for adsorbing bone morphogenetic protein onto a cation-exchange resin (e.g., SP Sepharose), a process for washing the resin with 0.5-5.0M sodium chloride solution, and a process for eluting bone morphogenetic protein adsorbed on the resin with 4-8M guanidine hydrochloride. In case the animal cell culture medium supernatant contains dextran sulfate, the supernatant is passed through an anion-exchange resin (Q Sepharose) prior to the cation-exchange resin to remove dextran sulfate. Bone morphogenetic protein is **human MP52**, BMP-2, BMP-4, BMP-6, or BMP-7.

L8 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

1999:811377 Document No. 132:45828 Method of screening for low molecular weight compounds with morphogenetic activity by using **human MP52** gene promoter. Kawai, Shinji; Sugiura, Takeyuki; Hotten, Gertrud (Hoechst Marion Roussel Ltd., Japan). PCT Int. Appl. WO 9966060 A1 19991223, 24 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IB1071 19990611. PRIORITY: JP 1998-170941 19980618.

AB The present invention provides a method for exploring low mol. weight compds. with osteogenetic activity or osteogenesis inhibitory activity comparable to human bone morphogenic proteins (BMP). By screening for low mol. weight compds. which regulate pos. or neg. the expression of **human MP52** through monitoring the reporter gene activity in animal cells transformed with a recombinant expression vector into which 5' upstream region of **human MP52** gene containing the **human MP52** promoter has been ligated to an appropriate reporter gene, the method can be accomplished. Low mol. weight compds. and their derivs. obtained by the present method may have osteogenetic or osteogenesis inhibitory activity, neurogenic activity, or angiogenic/anti-angiogenic activity, and can be effective as preventive or therapeutic agent for cartilage and bone diseases, therapeutic agent for injury of tendon and

ligament, therapeutic agent for neural diseases, or healing agent for injury and carcinostatic, through the expression of **human MP52.**

L8 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
1999:764189 Document No. 132:9630 Expression of mutant recombinant **human MP52** protein monomer with bone morphogenetic activity and its use for preventing and treating cartilage and bone diseases. Kawai, Shinji; Kimura, Michio; Muraki, Yoshifumi; Katsuura, Mieko (Hoechst Marion Roussel Ltd., Japan). PCT Int. Appl. WO 9961611 A1 19991202, 26 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IB866 19990514. PRIORITY: JP 1998-141379 19980522.
AB A mutant recombinant **human MP52** protein monomer belonging to TGF-β superfamily with two-fold higher activity for inducing osteoblast cell line differentiation was created by site-directed mutagenesis replacing a cysteine contributing to dimer formation with another amino acid. Another amino acid replacing a cysteine can be serine, threonine, alanine, or valine, and preferably alanine. The mutant recombinant protein can be expressed in Escherichia coli, yeast, insect cells, and mammalian cells that have been transformed with an expression vector having a DNA sequence coding for the monomer protein. The use of the mutant recombinant **human MP52** protein monomer for prevention and therapeutic treatment of bone and/or cartilage diseases such as osteoporosis, osteoarthritis or arthrosteitis, bone fracture, and lack of teeth root or tooth socket is claimed.

L8 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
1998:542980 Document No. 129:140696 Freeze-dried composition of bone morphogenetic protein **human mp52.** Inagaki, Mitsuko; Ichikawa, Hideki (Hoechst Marion Roussel Ltd., Japan). PCT Int. Appl. WO 9833514 A1 19980806, 10 pp. DESIGNATED STATES: W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP371 19980129. PRIORITY: JP 1997-16349 19970130.
AB The invention relates to a stable freeze-dried composition of a bone morphogenetic protein **human MP52** wherein coloration and shrinking of MP52 during storage and aggregation at the re-dissoln. can be prevented. The composition is obtained by mixing MP52 with mannitol at a weight ratio of 1 : 5 to 1 : 50 followed by freeze-drying.

L8 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
1997:757113 Document No. 128:21872 Preparation of anti-dimeric **human MP52** monoclonal antibody. Kitagawa, Hiroshi; Jitsukawa, Tomofumi; Nakagawa, Hiraku; Yanagisawa, Sachiko (Hoechst Pharmaceuticals and Chemicals K.K., Japan). PCT Int. Appl. WO 9743408 A1 19971120, 46 pp. DESIGNATED STATES: W: AL, AU, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1997-JP1603 19970513. PRIORITY: JP 1996-141137 19960513; JP 1997-131631 19970507.
AB A mouse anti-human bone morphogenic factor MP52 monoclonal antibody which binds to dimeric **human MP52** but not to monomeric **human MP52** is prepared This IgG type mouse monoclonal antibody is highly specific and is not cross reactive to other bone morphogenic factors of the TGF-β gene superfamily. The monoclonal

antibody can be obtained by sensitizing mice with **human MP52** (CHO-MP52) produced in CHO cells or **human MP52** (rhMP52) produced in Escherichia coli. This antibody is useful in, for example, purifying or assaying **human MP52** produced by genetic engineering techniques.

L8 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
1997:740329 Document No. 128:21929 Process for producing maturation bone morphogenetic protein. Takahashi, Mikiko; Makishima, Fusao; Kimura, Michio (Hoechst Pharmaceuticals & Chemicals K. K., Japan; Takahashi, Mikiko; Makishima, Fusao; Kimura, Michio). PCT Int. Appl. WO 9741250 A1 19971106, 34 pp. DESIGNATED STATES: W: AU, CA, CN, CZ, HU, IL, KR, MX, NO, PL, RU, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1997-JP1474 19970428. PRIORITY: JP 1996-130618 19960430.
AB A process for producing a matured bone morphogenetic protein with a processing enzyme on a bone morphogenetic protein precursor, which comprises either introducing an expression vector of a bone morphogenetic protein precursor and an expression vector of a processing enzyme into an animal cell strain, culturing the resultant strain to yield a matured bone morphogenetic protein, and separating the same from the culture, or alternatively adding a solution of a processing enzyme to a solution of a bone morphogenetic protein precursor and incubating the obtained solution mixture A suitable process comprises introducing an expression vector (pMSS99) of a **human MP52** precursor and an expression vector (pDfurpRC/CMV) of a secretory furin variant into an established animal cell line CHO, culturing the resultant CHO cell to yield a matured bone morphogenetic protein, and separating the same from the culture.

L8 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
1997:244334 Document No. 126:221079 **Human MP52** protein, its manufacture with recombinant cells, and its use in pharmaceuticals. Kimura, Michio; Matsumoto, Tomoaki; Takahashi, Mikiko; Kawai, Shinji; Fujino, Yukio (Biopharm Gesellschaft Zur Biotechnologischen Entwicklung von Pharmaka mbH, Germany). PCT Int. Appl. WO 9706254 A1 19970220, 25 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-EP3427 19960802. PRIORITY: EP 1995-112241 19950803.
AB This invention relates to a **human MP52** Arg and a pharmaceutical medical composition inter alia for promoting cartilage and bone morphogenation comprising **human MP52** Arg. In particular, the medical composition is useful for treating bone disease caused by abnormal bone metabolism such as osteoporosis, for treating bone fracture and for the purpose of orthopedic reconstruction, bone transplantation, cosmetic surgery and dental therapeutics. Further, it is useful for treating cartilage disorders. Recombinant CHO cells expressing prepro-human MP42 were prepared and cultured to obtain recombinant MP52. Treatment of ROB-C26 cells with the MP52 increased total alkaline phosphatase activity in a concentration-dependent manner.

L8 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
1996:732173 Document No. 126:1703 Recombinant preparation of dimeric human protein MP52 and use for treating bone diseases. Makishima, Fusao; Takamatsu, Hiroyuki; Miki, Hideo; Kawai, Shinji; Kimura, Michio; Matsumoto, Tomoaki; Katsuura, Mieko; Enomoto, Koichi; Satoh, Yusuke (Hoechst Japan Limited, Japan). PCT Int. Appl. WO 9633215 A1 19961024, 33 pp. DESIGNATED STATES: W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN:

PIXXD2. APPLICATION: WO 1996-JP1062 19960419. PRIORITY: JP 1995-93664 19950419; JP 1995-322403 19951117.
AB Methods for recombinant preparation of mature monomeric human protein MP52 (119 amino acids) in transgenic Escherichia coli followed by chemical dimerization of the protein are disclosed. Biol. effects of the dimer on stimulating the growth of bones or cartilage were also demonstrated. This dimer protein is useful in the treatment of cartilage and bone diseases.

=> s human BMP5
L9 8 HUMAN BMP5

=> s l9 and modified
L10 0 L9 AND MODIFIED

=> dup remove l9
PROCESSING COMPLETED FOR L9
L11 8 DUP REMOVE L9 (0 DUPLICATES REMOVED)

=> d s l9 and monomeric
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'AND' IS NOT A VALID FORMAT
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'D' IS NOT A VALID FORMAT
'HIS' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid in at least one of the files. Refer to file specific help messages or the STNGUIDE file for information on formats available in individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):cbib abs

L9 ANSWER 1 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2006:120134 Document No.: PREV200600116235. A quantitative trait locus for bicuspid aortic valve and associated cardiac anomalies localizes to chromosome 6p. Martin, L. J. [Reprint Author]; Cripe, L.; Andelfinger, G.; Tabangin, M.; Shooner, K.; Benson, D. W.. Univ Cincinnati, Childrens Hosp, Cincinnati, OH 45221 USA. Genetic Epidemiology, (NOV 2005) Vol. 29, No. 3, pp. 267.
Meeting Info.: 14th Annual Meeting of the International-Genetic-Epidemiology-Society. Park City, UT, USA. October 23 -24, 2005. Int Genet Epidemiol Soc.
ISSN: 0741-0395. Language: English.

=> s l9 and monomeric
L12 0 L9 AND MONOMERIC

=> s human BMP-6
L13 40 HUMAN BMP-6

=> s l13 and substitution
L14 0 L13 AND SUBSTITUTION

=> s l13 and cysteine
L15 0 L13 AND CYSTEINE

=> s l13 and monomeric
L16 0 L13 AND MONOMERIC

=> s human BMP-7

L17 76 HUMAN BMP-7

=> s l17 and monomeric
L18 0 L17 AND MONOMERIC

=> s BMP-5
L19 297 BMP-5

=> s l19 and monomeric
L20 0 L19 AND MONOMERIC

=> s BMP-6
L21 969 BMP-6

=> s l21 and monomeric
L22 0 L21 AND MONOMERIC

=> s BMP-7
L23 2215 BMP-7

=> s l23 and monomeric
L24 7 L23 AND MONOMERIC

=> dup remove l24
PROCESSING COMPLETED FOR L24
L25 3 DUP REMOVE L24 (4 DUPLICATES REMOVED)

=> d l25 1-3 cbib abs

L25 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
2001671369. PubMed ID: 11716552. Cerebrospinal fluid contains biologically active bone morphogenetic protein-7. Dattatreyamurty B; Roux E; Horbinski C; Kaplan P L; Robak L A; Beck H N; Lein P; Higgins D; Chandrasekaran V. (Creative Biomolecules Inc., Hopkinton, Massachusetts 01748, USA.) Experimental neurology, (2001 Dec) 172 (2) 273-81. Journal code: 0370712. ISSN: 0014-4886. Pub. country: United States. Language: English.

AB Bone morphogenetic proteins (BMPs) regulate the development and function of many types of neurons. However, little is known of the actual concentrations of BMPs in the various parts of the brain. In this study, we considered the possibility that BMPs might be present in cerebrospinal fluid (CSF). Western blot analysis of normal adult bovine CSF revealed the presence of dimeric and **monomeric** forms of **BMP-7**, and the concentration of this molecule was found to be approximately 12 ng/ml in a radioimmunoassay. Since **BMP-7** is known to induce dendritic growth in rat sympathetic neurons, this was used as a bioassay to examine the biological activity of the **BMP-7** present in CSF. Addition of normal bovine CSF to cultures of sympathetic neurons produced a dose-dependent increase in dendritic growth and the magnitude of this response approximated that obtained with maximally effective concentrations of exogenous **BMP-7**. Moreover, CSF-induced dendritic growth was inhibited by follistatin, a protein that can sequester BMPs, and by either of two monoclonal antibodies that react with **BMP-7**. These results show that, unlike most other neurotrophic factors, **BMP-7** is a constituent of normal CSF and is present at concentrations sufficient to elicit a near maximal biological response.

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
1997:687801 Document No. 127:344050 Genes and biological functions of bone morphogenetic proteins. Ueno, Naoto; Nishimatsu, Shin-ichiro; Shoda, Akihito; Suzuki, Atsushi; Takebayashi, Kimiko; Yamagishi, Toshiyuki; Murakami, Kazuo (School of Pharmacology, Hokkaido University, Japan). Journal of Hard Tissue Biology, 5(2), 110-118 (English) 1996. CODEN: JHTBFF. ISSN: 1341-7649. Publisher: Japanese Society of Hard Tissue

Research & Technology.

AB The authors have previously demonstrated that activin, a member of the TGF-β family, has a potent mesoderm-inducing activity in Xenopus embryos. Activin can efficiently induce mesoderm formation that is associated with E.vphi.-activin gene activation when applied to the culture of isolated presumptive ectoderm (animal cap). In the course of screening for activin-related genes from Xenopus, the authors isolated a gene which predicts a protein which is extremely similar to human BMP-2(bone morphogenetic protein-2) which had previously been shown to induce ectopic bone formation. Subsequently, the authors have cloned cDNAs for Xenopus homolog of BMP-2, -4 and -7. Deduced protein structure of Xenopus BMP-2, -4 and 7 suggested that they all are synthesized as large precursor proteins of 398, 401, 428 amino acids, and processed to mature proteins of 114, 114, and 428 amino acids. Northern blot anal. revealed that these BMP genes are maternally encoded and differentially regulated after fertilization. Polyclonal antibodies capable of reaction with the Xenopus BMP-2 (xBMP-2) and -4 (xBMP-4) were raised in rabbits by immunization with a synthetic 21 amino acid peptide which corresponds to a sequence residues in the mature protein of xBMP-2. The antibodies recognized both xBMP-2 and xBMP-4 equally but did not recognize recombinant human BMP-3, 5, nor 6. The antibodies designated Ab383 could detect an embryonic BMP as well as mammalian and bacteria expressed recombinant xBMPs. The antibodies detected, under reducing conditions, a 30 kDa protein in the extract of oocytes and embryos during early development. Interestingly, acidification of the extract from each developmental stage yielded a protein band of smaller mol. weight of 18 kDa, which is similar in size to reduced form of mature BMPs purified from mammalian species. Two dimensional electrophoresis employed to examine the mol. weight of unreduced forms using the antibody, revealed that both mol. forms are **monomeric** in the embryos. The result suggests that at least BMP-2 mRNA previously detected in early embryos, is translated into peptide but the dimerization may be incomplete or strictly limited in these embryos. Specific antibodies to Xenopus laevis bone morphogenetic protein-4 (xBMP-4) were also raised by immunizing rabbits with a fusion protein of bacterial galactosidase and xBMP-4. The antibodies were used to detect xBMPs expressed in mammalian cells by Western blotting. The antibodies were found to recognize xBMP-4 specifically and not to cross-react with either xBMP-2 or xBMP-7 which are similar to xBMP-7. In addition, the antibodies recognized dimeric xBMP-4 whereas Ab3783 recognized the reduced form only. The BMP-4 specific antibodies, Ab97 an immunoreactive 27-kDa protein in exts. of developing Xenopus embryos from oocyte to tailbud embryo. In addition to xBMP-2, the xBMP-4 peptide also appeared to be **monomeric** in structure because the mol. weight did not shift upon reduction of disulfide bonds(s). The

Ab383 were further used to detect high mol. weight forms of Xenopus BMP-2. Partial purification of the immunoreactive 18 kDa BMP-2 from Xenopus embryo extract by gel filtration, heparin-Sepharose affinity chromatog. and preparative SDS-PAGE resulted in copurifn. and identification of higher mol. forms of BMP-2 of 110 kDa and 36 kDa. Diagonal SDS-PAGE anal. suggested that they are homodimer and multimer of the 18 kDa species, resp., linked through disulfide bridge(s). The biochem. properties of recombinant protein of the Xenopus BMP-4 was also characterized. The protein was expressed by the transection of Chinese hamster ovary (CHO) cells with the cDNA cloned into expression vectors bearing a cytomegalovirus promoter of a simian virus 40 promoter. Northern blot anal. showed that the latter vector was more efficient for xBMP-4 peptide (Ab97) demonstrated that as expected, the protein is synthesized as a large precursor, processed to mature form and then secreted from the cells as a homodimer (Fig. 8). It was previously shown that alkaline phosphatase (ALPase) activity is induced in a mouse osteoblastic cell line, MC3T3-E1 cells treated with BMP-2. The ALPase-inducing assay using the recombinant BMP proteins secreted into the culture medium of COS cells transfected with Xenopus BMP cDNAs has shown that at least BMP-2 and-4 have similar ALPase-inducing activity to mammalian counterparts. Anal. of the biol. activity in the partially purified conditioned medium from CHO cells

transfected with BMP-4 cDNA also revealed that xBMP-4 has the ALPase-inducing activity. Besides the biol. activity related to cell differentiation, BMP-4 was found to affect morphogenesis in early development. When mRNA of Xenopus BMP-4 was injected into dorsal blastomeres of Xenopus embryos, formation of anterior and dorsal structures of the injected embryos were severely perturbed. The results suggests that BMP-4 has a ventralizing activity and that the activity as well as dorsalizing activity probably represented by activin, is important in the pattern formation of developing embryo. Expression levels of mRNA for Xenopus BMPs in adult organs were examined using reverse transcription-polymerase chain reaction (RT-PCR) that used specific primers for each BMP subtype. The sensitive method to detect minute amts. of RNA revealed that mRNAs for BMP-2 and BMP-4 are disturbed in a wide variety of adult tissues including lung, heart, and kidney. Unexpectedly, distribution of mRNA for **BMP**-7 was found to be limited to ovary and early embryos. The result suggests that Xenopus **BMP** -7 may have a specific role in ovary and early embryos. By whole mount in situ hybridization, it was shown that genes for BMP-2 and -4 are temporally and spatially regulated during embryogenesis. Finally, the authors propose that BMPs are the multifunctional growth factors which regulate not only cell differentiation but also axis formation in normal development. The authors would like to emphasize that in addition to bone-inducing activity, the latter function related to planning is essential in vertebrates.

L25 ANSWER 3 OF 3 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:117222 The Genuine Article (R) Number: QF459. OSTEOGENIC PROTEIN-1 (OP-1) EXPRESSION AND PROCESSING IN CHINESE-HAMSTER OVARY CELLS - ISOLATION OF A SOLUBLE COMPLEX CONTAINING THE MATURE AND PRO-DOMAINS OF OP-1. JONES W K (Reprint); RICHMOND E A; WHITE K; SASAK H; KUSMIK W; SMART J; OPPERMANN H; RUEGER D C; TUCKER R F. CREAT BIOMOLEC, 35 S ST, HOPKINTON, MA 01748 (Reprint). GROWTH FACTORS (1994) Vol. 11, No. 3, pp. 215-225. ISSN: 0897-7194. Publisher: TAYLOR & FRANCIS LTD, 4 PARK SQUARE, MILTON PARK, ABINGDON OX14 4RN, OXON, ENGLAND. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We have characterized the expression and processing of Osteogenic Protein-1 (hOP-1), a bone morphogenic protein of the TGF-beta family, in Chinese hamster ovary cells. The hOP-1 is initially synthesized as a **monomeric** 50 kDa pro-protein that is dimerized, glycosylated, and then proteolytically cleaved at the Arg-Xaa-Xaa-Arg maturation site in an acidic cellular compartment before secretion into the medium. Of the four potential N-linked glycosylation sites two are used, one in the mature domain and one in the pro-domain. Gel permeation chromatography of secreted hOP-1 in physiological buffers yields an apparent molecular weight of 110-120 k, indicating that after proteolytic processing the two pro-domains remain non-covalently associated with the disulfide linked mature dimer in a complex termed soluble hOP-1 Purified soluble hOP-1 is significantly more soluble in physiological buffers than the purified mature OP-1.

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=> s BMP-8
L26          55 BMP-8

=> s l26 and monomeric
L27           0 L26 AND MONOMERIC

=> s BMP-12
L28          92 BMP-12

=> s l28 and monomeric
L29           0 L28 AND MONOMERIC

=> s BMP-13
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L30 53 BMP-13

=> s l30 and monomeric
L31 0 L30 AND MONOMERIC

=> s BMP-14
L32 17 BMP-14

=> s l32 and monomeric
L33 0 L32 AND MONOMERIC

=> s BMP-52
L34 0 BMP-52

=> s GDF-5
L35 398 GDF-5

=> s l35 and monomeric
L36 1 L35 AND MONOMERIC

=> d l36 cbib abs

L36 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2001:98512 Document No. 134:142803 Method for producing human **monomeric** proteins of the TGF-beta family. (Mader & Baumgartner Treuhand A.-G., Switz.). Eur. Pat. Appl. EP 1074620 A1 20010207, 31 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-115613 19990806.

AB The present invention is concerned with a method for producing human proteins selected from the members of the TGF-β superfamily, which are **monomeric** due to substitution or deletion of a cysteine which is responsible for dimer formation. The invention is also concerned with nucleic acids, encoding such **monomeric** proteins, vectors or host cells containing the nucleic acids as well as with pharmaceutical compns. comprising the proteins or nucleic acids encoding the proteins. The pharmaceutical compns. can be applied advantageously for all indications for which the resp. dimeric proteins are useful.

=> s GDF-6
L37 54 GDF-6

=> s l37 and monomeric
L38 0 L37 AND MONOMERIC

=> s GDF-7
L39 56 GDF-7

=> s l39 and monomeric
L40 0 L39 AND MONOMERIC

=> s TGF beta
L41 121327 TGF BETA

=> s l41 and monomeric
L42 171 L41 AND MONOMERIC

=> s l41 and amino acid substitution
L43 212 L41 AND AMINO ACID SUBSTITUTION

=> s l

L44 4259794 L

=> s l42 and substitution
L45 5 L42 AND SUBSTITUTION

=> dup remove l45
PROCESSING COMPLETED FOR L45
L46 2 DUP REMOVE L45 (3 DUPLICATES REMOVED)

=> d l46 1-2 cbib abs

L46 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
2001:98512 Document No. 134:142803 Method for producing human **monomeric** proteins of the **TGF-beta** family. (Mader & Baumgartner Treuhand A.-G., Switz.). Eur. Pat. Appl. EP 1074620 A1 20010207, 31 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-115613 19990806.

AB The present invention is concerned with a method for producing human proteins selected from the members of the **TGF**-β superfamily, which are **monomeric** due to **substitution** or deletion of a cysteine which is responsible for dimer formation. The invention is also concerned with nucleic acids, encoding such **monomeric** proteins, vectors or host cells containing the nucleic acids as well as with pharmaceutical compns. comprising the proteins or nucleic acids encoding the proteins. The pharmaceutical compns. can be applied advantageously for all indications for which the resp. dimeric proteins are useful.

L46 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1
89340446. PubMed ID: 2474534. Site-directed mutagenesis of cysteine residues in the pro region of the transforming growth factor beta 1 precursor. Expression and characterization of mutant proteins. Brunner A M; Marquardt H; Malacko A R; Lioubin M N; Purchio A F. (Oncogen, Seattle, Washington 98121.) Journal of biological chemistry, (1989 Aug 15) 264 (23) 13660-4. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Three cysteine residues are located in the pro region of the transforming growth factor beta 1 (**TGF-beta** 1) precursor at amino acid positions 33, 223, and 225. Previous studies (Gentry, L. E., Lioubin, M. N., Purchio, A. F., and Marquardt, H. (1988) Mol. Cell. Biol. 8, 4162-4168) with purified recombinant **TGF-beta** 1 (rTGF-beta 1) precursor produced by Chinese hamster ovary (CHO) cells revealed that Cys-33 can form a disulfide bond with at least 1 cysteine residue in mature **TGF-beta** 1, contributing to the formation of a 90-110-kDa protein. We now show that Cys-223 and Cys-225 form interchain disulfide bonds. Site-directed mutagenesis was used to change these Cys codons to Ser codons, and mutant constructs were transfected into COS cells. Analysis of recombinant proteins by immunoblotting showed that by substituting Cys-33 the 90-110-kDa protein is not formed, and thus, more mature dimer (24 kDa) is obtained, corresponding to a 3- to 5-fold increase in biological activity. **Substitution** of Cys-223 and/or Cys-225 resulted in near wild-type levels of mature **TGF-beta** 1. Furthermore, cells transfected with plasmid coding for Ser at positions 223 and 225 expressed only **monomeric** precursor proteins and released bioactive **TGF-beta** 1 that did not require acid activation, suggesting that dimerization of the precursor pro region may be necessary for latency.

=> s (kawai s?/au or kimura m?/au or muraki y?/au or katsuura M?/au)
L47 31202 (KAWAI S?/AU OR KIMURA M?/AU OR MURAKI Y?/AU OR KATSUURA M?/AU)

=> s l47 and monomeric protein
L48 0 L47 AND MONOMERIC PROTEIN

=> s l47 and TGF beta
L49 63 L47 AND TGF BETA

=> s l49 and monomeric
L50 0 L49 AND MONOMERIC

=> s l49 and human MP52
L51 1 L49 AND HUMAN MP52

=> d l51 cbib abs

L51 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
1999:764189 Document No. 132:9630 Expression of mutant recombinant **human MP52** protein monomer with bone morphogenetic activity and its use for preventing and treating cartilage and bone diseases. **Kawai, Shinji; Kimura, Michio; Muraki, Yoshifumi; Katsuura, Mieko** (Hoechst Marion Roussel Ltd., Japan). PCT Int. Appl. WO 9961611 A1 19991202, 26 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IB866 19990514. PRIORITY: JP 1998-141379 19980522.

AB A mutant recombinant **human MP52** protein monomer belonging to **TGF**-β superfamily with two-fold higher activity for inducing osteoblast cell line differentiation was created by site-directed mutagenesis replacing a cysteine contributing to dimer formation with another amino acid. Another amino acid replacing a cysteine can be serine, threonine, alanine, or valine, and preferably alanine. The mutant recombinant protein can be expressed in Escherichia coli, yeast, insect cells, and mammalian cells that have been transformed with an expression vector having a DNA sequence coding for the monomer protein. The use of the mutant recombinant **human MP52** protein monomer for prevention and therapeutic treatment of bone and/or cartilage diseases such as osteoporosis, osteoarthritis or arthrosteitis, bone fracture, and lack of teeth root or tooth socket is claimed.

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